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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/928,872	08/13/2001	Richard Kolesnick	6923-106	8412

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	15

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/928,872	KOLESNICK ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears n the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/9/03; 4/9/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,7 and 9-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7 and 9-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/9/03 has been entered.

2. Claims 1-3, 5, 7 and 9-13 are pending and being acted upon in this Office Action.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

4. Claims 2-3 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "exposing the cell" in claims 2 and 5 part (b) is ambiguous, indefinite and one of ordinary skill in the art cannot appraise the metes and bound of the claimed invention because it is not clear which cell such as the cell deficient acid sphingomyelinase activity or the cell exhibiting normal acid sphingomyelinase activity is being exposed.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless:
>
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-2, 5, and 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jaffrezou *et al* (Cancer Research 52: 6440-6446, December 1992; PTO 892) in view of Lowe *et al* (of record, Cell 74: 957-967, Sept 1993; PTO 1449), Jarvis *et al* (of record, Proc. Natl. Acad Sci USA: 91: 73-77, Jan 1994: PTO 1449), Cifone *et al* (of record, EMBO J 14(23): 5859-68, 1995; PTO 1449) and Cifone *et al* (J Exp Med 180(4): 1547-52, Oct 1994; PTO 892).

Jaffrezou *et al* teach a method of identifying compound which increase or decrease a cell's sensitivity to acid sphingomyelinase (ASMase) related multidrug resistant by contacting various cell line such as P388/ADR cell which are dororubicin-resistant, P388 parent cells which are doxorubicin-sensitive, NPD cell line such as TRE and ALB which acid sphingomyelinase deficient (See page 6441, column 1, first paragraph, column 2, last paragraph, in particular) with a chemotherapeutic agent such as doxorubicin (Dox) in the absence or presence of a test compound such as SR33557, which is a lysosomal acid sphingomyelinase inhibitor, (see page 6443, column 1, first full paragraph, in particular) and monitoring the exposed cells for morphological changes such as distribution of Dox, SR3357 and fluorescent probe Lucifer yellow (See page Fig 2, caption, in particular). Jaffrezou *et al* teach that lysosomal acid sphingomyelinase inhibitor such as SR33557 may modulate subcellular distribution of chemotherapeutic agent associated with multidrug-resistant with morphological modification similar to those observed in Niemann-Pick disease lymphoblastoid cell lines which are inherently deficient in acid sphingomyelinase activity (See abstract, in particular).

The claimed invention in claim 1 differs from the teachings of the reference only the method wherein the method monitoring the exposed cells for exhibiting apoptotic morphology and compared to that of the control.

The claimed invention in claim 2 differs from the teachings of the reference only the method wherein the method monitoring the exposed cells for the levels of sphingomyelinase or

the levels of ceramide and if the sphingomyelin is decrease while the level of ceramide increases in cell exposed to chemotherapeutic agent as compared to the control, the test compound represents a compound, which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

The claimed invention in claim 5 differs from the teachings of the reference only the method wherein the method monitoring the exposed cells for the levels of sphingomyelinase or the levels of ceramide and comparing the levels of sphingomyelin and ceramide and if the sphingomyelin level is greater while ceramide level is less than the control, the test compound represents a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

The claimed invention in claims 9 differs from the teachings of the reference only that the method wherein the apoptotic morphology comprises cellular condensation, nuclear condensation and zeiosis.

Lowe *et al* teaches that the chemotherapeutic agent such as ionizing radiation induced apoptosis (See Figs 2-6, page 965, Experimental procedure, in particular) wherein the apoptotic morphology comprises cellular condensation, nuclear condensation or zeiosis. (See page 960, column 2, first full paragraph, Fig 6, in particular). Lowe *et al* teaches that ionizing radiation and several chemotherapeutic agents trigger apoptosis in cells expression the p53 tumor suppressor, while having little or no effects on the viability of cells lacking p53, which is the control (See page 963, column 1, Figure 3, in particular). Lowe *et al* teach the use of genetic approach such as $p53^{+/+}$ wild type and $p53^{-/-}$ deficient cell lines to monitor cell's sensitivity to chemotherapeutic agent such as radiation induces apoptosis (See entire document, Table 1, in particular).

Jarvis *et al* teach that when cells such as HL60 and U937 that exhibiting acid sphingomyelinase activity are exposed to various chemotherapeutics stress such as sphingomyelinase and C8ceramide, the cells undergo apoptosis (See entire document, Figs 1, 3 and 6, in particular). Jarvis *et al* teach how to determine the morphological features of apoptosis such as cellular condensation, nuclear condensation or zeiosis (See Fig 6, Materials and Methods, in particular).

Cifone *et al* (EMBO J 14(23): 5859-68, 1995; PTO 1449) teach that both acid and neutral sphingomyelinase contribute to TNF mediated apoptosis (See page 5864, Figure 7A, filled bars, in particular). Cifone *et al* teach that when cells such as HuT78 that exhibits acid sphingomyelinase activity are exposed to chemotherapeutics agent such as crosslinking Fas

receptor using anti-Fas antibody or TNF, apoptotic cell death results. This is associated with a decrease in the level of sphingomyelin (breakdown) with a concomitant increase in the level of ceramide (generation) (See Figs 2-4, 7, page 5865-5866, Materials and methods, in particular). Cifone *et al* further teach how to measure the levels of ceramide and sphingomyelin (See page 5866, column 1, in particular). Cifone *et al* teach that acid sphingomyelinase activation is a key step for the propagating of the death signal (See page 5860, column 2, last paragraph, in particular) and it is of interest to screen for compound which increase or decrease the cell's sensitivity to acid sphingomyelinase related apoptosis (See page 5865, column 2, Biological implications, in particular).

Cifone *et al* (J Exp Med 180(4): 1547-52, Oct 1994; PTO 892) teach that apoptotic signaling through CD95 (Fas/Apo-1) using a chemotherapeutic agent such as DX2 which is a functional anti-CD95 monoclonal antibody activates acidic sphingomyelinase in promyelocytic U937 cells 9 (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to identify any compound which increase or decrease a cell's sensitivity to acid sphingomyelinase-related apoptosis by substituting the P388/ADR cell and P388 cells as taught by Jaffrezou *et al* or the p53 deficient cells as taught by Lowe *et al* for the sphingomyelinase deficient cell line from NPD such as TRE and ALB as taught by Jaffrezou *et al* and determine the apoptotic morphology as taught by Lowe *et al,* or determine the levels of sphingomyelinase and ceramide as taught by Jarvis *et al* and Cifone *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Jarvis *et al* teach acid sphingomyelinase induces cell death by apoptosis in cells exhibiting acid sphingomyelinase activity (See entire document, Figs 1, 3 and 6, in particular). Cifone *et al* (EMBO J 14(23): 5859-68, 1995; PTO 1449) teach that acid sphingomyelinase activation is a key step for the propagating of the death signal (See page 5860, column 2, last paragraph, in particular) and it is of interest to screen for compound which increase or decrease the cell's sensitivity to acid sphingomyelinase related apoptosis (See page 5865, column 2, Biological implications, in particular).

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Cifone *et al* (teach that it is of interest to screen for compound which

increase or decrease the cell's sensitivity to acid sphingomyelinase related apoptosis (See page 5865, column 2, Biological implications, in particular). Jarvis *et al* teach that cell exhibiting acid sphingomyelinase when exposed to chemotherapeutic agent can induce cell death by apoptosis and cell undergoing apoptosis can be determine by the morphological features such as cellular condensation, nuclear condensation or zeiosis (See Fig 6, Materials and Methods, in particular). Lowe *et al* teaches that the chemotherapeutic agent such as ionizing radiation induced apoptosis (See Figs 2-6, page 965, Experimental procedure, in particular) wherein the apoptotic cell exhibit morphology such as cellular condensation, nuclear condensation or zeiosis (See page 960, column 2, first full paragraph, Fig 6, in particular) using genetic approach such as $p53^{+/+}$ wild type and $p53^{-/-}$ deficient cell lines (See entire document, Table 1, in particular). Jaffrezou *et al* teach that lysosomal acid sphingomyelinase inhibitor such as SR33557 may modulate subcellular distribution of chemotherapeutic agent associated with multidrug-resistant with morphological modification similar to those observed in Niemann-Pick disease lymphoblastoid cell lines which are inherently deficient in acid sphingomyelinase activity (See abstract, in particular). Cifone *et al* teach that apoptotic signaling through CD95 (Fas/Apo-1) using a chemotherapeutic agent such as DX2 which is a functional anti-CD95 monoclonal antibody activates acidic sphingomyelinase in promyelocytic U937 cells 9 (See abstract, in particular).

Applicants' arguments and the Jaffrezou and Segui references filed 4/9/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) Lowe does not teach methods to identify any compounds. While the present invention and Lowe both involve exposing a cell to chemotherapeutic agents, the critical difference between the present invention and Lowe is that Lowe fails to teach or suggest identifying test compounds which modulate a cell's sensitivity to chemotherapeutic agents; (2) None of the chemotherapeutic compounds such as 5-fluoroaucil, etoposide, and adriamycin are chemotherapeutic stress stimuli and not test compounds as taught by Lowe directly affected p53 or its pathway; (3) The present invention involves in test compounds that are selected based on their ability to affect the acid sphingomyelinase pathway. (4) Javis et al does not teach acid sphingomyelinase and only neutral sphingomyelinase is discussed; (5) At the time the invention of the present invention, acid sphingomyelinase was generally considered to be a lysosomal enzyme and ceramide produced by acid sphingomyelinase was thought not to be involved in apoptosis. (6) While Cifone discusses the potential role of acidic sphingomyelinase in apoptosis, the role of acidic sphingomyelinase in apoptosis was controversial and it was

generally accepted that acid sphingomyelinase was not involved in apoptosis. The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. In re Hedges, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986). The Jaffrezou and Segui references cited provided such as evidence. (7) There is no suggestion or motivation to modify the references. (8) There is not a reasonable expectation of success. As discussed above, the state of the art was not predictable at the time the invention was made. Thus, one of skill in the art would not have a reasonable expectation of success. (9) Not all the claims limitations are taught or suggested by the cited references.

In response to Applicants' argument in item 1, Jaffrezou *et al* teach a method of identifying compound which increase or decrease a cell's sensitivity to acid sphingomyelinase (ASMase) related multidrug resistant by contacting various cell line such as P388/ADR cell which are dororubicin-resistant, P388 parent cells which are doxorubicin-sensitive, NPD cell line such as TRE and ALB which acid sphingomyelinase deficient (See page 6441, column 1, first paragraph, column 2, last paragraph, in particular) with a chemotherapeutic agent such as doxorubicin (Dox) in the absence or presence of a test compound such as SR33557, which is a lysosomal acid sphingomyelinase inhibitor, (see page 6443, column 1, first full paragraph, in particular) and monitoring the exposed cells for morphological changes such as distribution of Dox, SR3357 and fluorescent probe Lucifer yellow (See page Fig 2, caption, in particular). Jaffrezou *et al* teach that lysosomal acid sphingomyelinase inhibitor such as SR33557 may modulate subcellular distribution of chemotherapeutic agent associated with multidrug-resistant with morphological modification similar to those observed in Niemann-Pick disease lymphoblastoid cell lines which are inherently deficient in acid sphingomyelinase activity (See abstract, in particular).

In response to Applicants' argument in item 2, Lowe *et al* teaches that the chemotherapeutic agent such as ionizing radiation induced apoptosis (See Figs 2-6, page 965, Experimental procedure, in particular) wherein the apoptotic morphology comprises cellular condensation, nuclear condensation or zeiosis (See page 960, column 2, first full paragraph, Fig 6, in particular). More importantly, Lowe *et al* teach the use of genetic approach such as $p53^{+/+}$ wild type and $p53^{-/-}$ deficient cell lines to determine a cell's sensitivity to chemotherapeutic agent such as radiation induces apoptosis (See entire document, Table 1, in particular).

In response to Applicants' argument in item 3, Jaffrezou *et al* teach a method of identifying compound which increase or decrease a cell's sensitivity to acid sphingomyelinase

(ASMase) related multidrug resistant by contacting various cell line such as P388/ADR cell which are dororubicin-resistant, P388 parent cells which are doxorubicin-sensitive, NPD cell line such as TRE and ALB which acid sphingomyelinase deficient (See page 6441, column 1, first paragraph, column 2, last paragraph, in particular) with a chemotherapeutic agent such as doxorubicin (Dox) in the absence or presence of a test compound such as SR33557, which is a lysosomal acid sphingomyelinase inhibitor, (see page 6443, column 1, first full paragraph, in particular). The claimed invention differs from the teachings of the reference only that the method wherein the method monitors the exposed cells for the present of an apoptotic morphology, the levels of sphingomyelinase or the levels of ceramide and compared that with the control. Lowe *et al* teaches that cell undergoing apoptosis induced by chemotherapeutic agent such as ionizing radiation exhibits apoptotic morphology such as cellular condensation, nuclear condensation or zeiosis (See page 960, column 2, first full paragraph, Fig 6, in particular). Likewise, Jarvis *et al* teach how to determine the morphological features of apoptosis such as cellular condensation, nuclear condensation or zeiosis (See Fig 6, Materials and Methods, in particular). Cifone *et al* further teach how to measure the levels of ceramide and sphingomyelin (See page 5866, column 1, in particular). Cifone *et al* teach that acid sphingomyelinase activation is a key step for the propagating of the death signal (See page 5860, column 2, last paragraph, in particular) and it is of interest to screen for compound which increase or decrease the cell's sensitivity to acid sphingomyelinase related apoptosis (See page 5865, column 2, Biological implications, in particular).

In response to Applicants' argument in items 4-6, although Javis et al does not teach acid sphingomyelinase and only neutral sphinogmyelinase is discussed, Cifone *et al* (EMBO J 14(23): 5859-68, 1995; PTO 1449) teach that both acid and neutral sphingomyelinase contribute to TNF mediated apoptosis (See page 5864, Figure 7A, filled bars, in particular). Cifone *et al* (J Exp Med 180(4): 1547-52, Oct 1994; PTO 892) teach that apoptotic signaling through CD95 (Fas/Apo-1) using a chemotherapeutic agent such as DX2 which is a functional anti-CD95 monoclonal antibody activates acidic sphingomyelinase in promyelocytic U937 cells 9 (See abstract, in particular). Further, it is known at the time the invention was made that apoptosis depends on a number of factors including cell type, stimuli and signaling pathways as evidences by the cited references.

In response to applicants' arguments that there is no suggestion to combine the references and there is not a reasonable expectation of success, the examiner recognizes that

obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). In this case the teachings of Jaffrezou *et al* pertaining to a method of identifying compound which increase or decrease a cell's sensitivity to acid sphingomyelinase (ASMase) related multidrug resistant, the teachings of Lowe *et al* indicating the success of using genetic approach such as $p53^{+/+}$ wild type and $p53^{-/-}$ deficient cell lines to identify p53 mediated apoptotic pathway (See entire document, Table 1, in particular), the teaching of Jarvis *et al* pertaining to determining the morphological features of apoptosis such as cellular condensation, nuclear condensation or zeiosis (See Fig 6, Materials and Methods, in particular) and the teachings of Cifone *et al* pertaining to determining the levels of sphingomyelinase activity where apoptosis is associated with a decrease in the level of sphingomyelin (breakdown) with a concomitant increase in the level of ceramide (generation) would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the analogous art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination, In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) See MPEP 2144.

In response to Applicants' argument in item 10, it is within the purview of one skill in the art at the time the invention was made to monitor the cells that have been exposed to chemotherapeutic agents for the presence of apoptotic morphology, to measure the levels of sphingomyelinase and the levels of ceramide and compared to that of the controls as taught by Lowe *et al* who teaches that ionizing radiation and several chemotherapeutic agents trigger apoptosis in cells expression the p53 tumor suppressor, while having little or no effects on the viability of cells lacking p53, which is the control (See page 963, column 1, Figure 3, in particular). Cifone *et al* teach that acid sphingomyelinase activation and generation of ceramide is a key step for the propagating of the death signal (See page 5860, column 2, last paragraph, in particular) and it is of interest to screen for compound which increase or decrease the cell's sensitivity to acid sphingomyelinase related apoptosis (See page 5865, column 2, Biological implications, in particular) by measuring the levels of sphingomyelin (breakdown or decrease)

with a concomitant increase in the level of ceramide (generation) (See Figs 2-4, 7, page 5865-5866, Materials and methods, page 5866, column 1, in particular).

8. Claims 3, 7, and 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jaffrezou *et al* (Cancer Research 52: 6440-6446, December 1992; PTO 892) in view of Lowe *et al* (of record, Cell 74: 957-967, Sept 1993; PTO 1449), Jarvis *et al* (of record, Proc. Natl. Acad Sci USA: 91: 73-77, Jan 1994: PTO 1449), Cifone *et al* (of record, EMBO J 14(23): 5859-68, 1995; PTO 1449) and Cifone *et al* (J Exp Med 180(4): 1547-52, Oct 1994; PTO 892) as applied to claims 1-2, 5, and 9-11 mentioned above and further in view of US Pat No 5,773,278 (of record, June 1998, PTO 892) or Horinouchi *et al* (of record, Nature Genetics 10: 288-293, July 1995; PTO 1449) or Otterbach *et al* (of record, Cell 81: 1053-61, June 1996; PTO 1449).

The combined teachings of Jaffrezou *et al,* Lowe *et al,* Jarvis *et al* and Cifone *et al* have been discussed supra.

The claimed invention in claim 3 differs from the reference only by the recitation of the acid sphingomyelinase-deficient cell is part of a genetically engineered nonhuman animal deficient for acid sphingomyelinase gene.

The claimed invention in claim 7 differs from the reference only by the recitation of the cell is part of a genetically engineered nonhuman animal deficient in endogenous acid sphingomyelinase gene activity and containing a functional human acid sphingomyelinase transgene capable of expressing functional human acid sphingomyelinase.

The claimed invention in claim 12 differs from the reference only by the recitation of the transgenic cells that are deficient in endogenous acid sphingomyelinase gene activity and contain a functional human acid sphingomyelinase gene.

The claimed invention in claim 13 differs from the reference only by the recitation of the cells are genetically engineered cells that exhibit greater level of acid sphingomyelinase activity than non-genetically engineered cells of the same type.

The '278 patent teaches acid sphingomyelinase deficient cell and cell line such as fibroblast or lymphoblasts generated from Niemann-Pick disease (NPD) patient and transgenic mice overexpressing the human acid sphingomyelinase gene (See column 27, lines 61-67, column 34, lines 17-30, in particular). The '278 patent teaches that nucleotide encoding for human acid sphingomyelinase (ASM) is useful for engineering transgenic mice and cell lines overexpressing

the human ASM for screening compound for treatment of Niemann-Pick disease (See column 7, lines 31-43, column 24, lines 46-58, in particular).

Horinouchi *et al* teach that acid sphingomyelinase deficient mice should be of great value for studying the pathogenesis and treatment of NPD and for investigations into the role of acid sphingomyelinase (ASMase) in signal transduction and apoptosis (See abstract, in particular).

Otterbach *et al* teach that acid sphingomyelinase deficient mice are useful as a model for the neurovisceral form of human Niemann-Pick disease (See entire document, Experimental Procedure, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the P388/ADR cell and P388 cells as taught by Jaffrezou *et al* or the p53 deficient cells as taught by Lowe *et al* for the transgenic cell lines that are deficient in endogenous acid sphingomyelinase gene activity and containing a functional human acid sphingomyelinase gene as taught by the '278 patent or the genetically engineered mice deficient for the acid sphingomyelinase as taught by Horinouchi *et al* or Otterbach *et al* for a method for identifying compound which increases or decreases a cell's sensitivity to sphingomyelinase-related apoptosis as taught by Jaffrezou *et al,* Lowe *et al,* Jarvis *et al*, Cifone *et al*, the '278 patent, Horinouchi *et al* and Otterbach *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '278 patent teaches that nucleotide encoding for human acid sphingomyelinase (ASM) is useful for engineering transgenic mice and cell lines to overexpress the human ASM for screening compound for treatment of Niemann-Pick disease (See column 7, lines 31-43, column 24, lines 46-58, in particular). Horinouchi *et al* teach that acid sphingomyelinase deficient mice should be of great value for studying the pathogenesis and treatment of NPD and for investigations into the role of acid sphingomyelinase (ASMase) in signal transduction and apoptosis (See abstract, in particular). Otterbach *et al* teach that acid sphingomyelinase deficient mice are useful as a model for the neurovisceral form of human Niemann-Pick disease (See entire document, Experimental Procedure, in particular).

Applicants' arguments and the Jaffrezou and Segui references filed 4/9/03 have been fully considered but are not found persuasive.

Applicants' position is that Shuchman, Horinouchi and Ottervach do not teach or suggest a method for identifying compounds that modulate acid sphingomyelinase-related apoptosis by exposing certain cells to a chemotherapeutic agent, as recited in all amended claims.

In response, the '278 patent teaches nucleotide encoding for human acid sphingomyelinase (ASM) is useful for engineering transgenic mice and cell lines overexpressing the human ASM for screening compound for treatment of Niemann-Pick disease (See column 7, lines 31-43, column 24, lines 46-58, in particular). Horinouchi *et al* teach that acid sphingomyelinase deficient mice should be of great value for studying the pathogenesis and treatment of NPD and for investigations into the role of acid sphingomyelinase (ASM) in signal transduction and apoptosis (See abstract, in particular). Otterbach *et al* teach that acid sphingomyelinase deficient mice are useful as a model for the neurovisceral form of human Niemann-Pick disease (See entire document, Experimental Procedure, in particular). Jaffrezou *et al* teach a method of identifying compound which increase or decrease a cell's sensitivity to acid sphingomyelinase (ASMase) related multidrug resistant by contacting various cell line such as P388/ADR cell which are dororubicin-resistant, P388 parent cells which are doxorubicin-sensitive, NPD cell line such as TRE and ALB which acid sphingomyelinase deficient (See page 6441, column 1, first paragraph, column 2, last paragraph, in particular) with a chemotherapeutic agent such as doxorubicin (Dox) in the absence or presence of a test compound such as SR33557, which is a lysosomal acid sphingomyelinase inhibitor, (see page 6443, column 1, first full paragraph, in particular) and monitoring the exposed cells for morphological changes such as distribution of Dox, SR3357 and fluorescent probe Lucifer yellow (See page Fig 2, caption, in particular). Jaffrezou *et al* teach that lysosomal acid sphingomyelinase inhibitor such as SR33557 may modulate subcellular distribution of chemotherapeutic agent associated with multidrug-resistant with morphological modification similar to those observed in Niemann-Pick disease lymphoblastoid cell lines which are inherently deficient in acid sphingomyelinase activity (See abstract, in particular).

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner

can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

11. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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Technology Center 1600
June 30, 2003

Applicants' position is that Shuchman, Horinouchi and Ottervach do not teach or suggest a method for identifying compounds that modulate acid sphingomyelinase-related apoptosis by exposing certain cells to a chemotherapeutic agent, as recited in all amended claims.

In response, the '278 patent teaches nucleotide encoding for human acid sphingomyelinase (ASM) is useful for engineering transgenic mice and cell lines overexpressing the human ASM for screening compound for treatment of Niemann-Pick disease (See column 7, lines 31-43, column 24, lines 46-58, in particular). Horinouchi *et al* teach that acid sphingomyelinase deficient mice should be of great value for studying the pathogenesis and treatment of NPD and for investigations into the role of acid sphingomyelinase (ASM) in signal transduction and apoptosis (See abstract, in particular). Otterbach *et al* teach that acid sphingomyelinase deficient mice are useful as a model for the neurovisceral form of human Niemann-Pick disease (See entire document, Experimental Procedure, in particular). Jaffrezou *et al* teach a method of identifying compound which increase or decrease a cell's sensitivity to acid sphingomyelinase (ASMase) related multidrug resistant by contacting various cell line such as P388/ADR cell which are dororubicin-resistant, P388 parent cells which are doxorubicin-sensitive, NPD cell line such as TRE and ALB which acid sphingomyelinase deficient (See page 6441, column 1, first paragraph, column 2, last paragraph, in particular) with a chemotherapeutic agent such as doxorubicin (Dox) in the absence or presence of a test compound such as SR33557, which is a lysosomal acid sphingomyelinase inhibitor, (see page 6443, column 1, first full paragraph, in particular) and monitoring the exposed cells for morphological changes such as distribution of Dox, SR3357 and fluorescent probe Lucifer yellow (See page Fig 2, caption, in particular). Jaffrezou *et al* teach that lysosomal acid sphingomyelinase inhibitor such as SR33557 may modulate subcellular distribution of chemotherapeutic agent associated with multidrug-resistant with morphological modification similar to those observed in Niemann-Pick disease lymphoblastoid cell lines which are inherently deficient in acid sphingomyelinase activity (See abstract, in particular).

9. No claim is allowed.

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